EXHIBIT "B"

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Heather Forgey, Esq.
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Premier Place
5910 N. Central Expressway, Suite 1700
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re: Campos v Safety-Kleen

Dear Ms. Forgey:

This report will summarize my opinions for the above cited case as it relates to Mr. Gerardo Campos' development of chronic myelogenous leukemia (CML) and his workplace with use of a Safety-Kleen parts washer with Safety-Kleen 105 solvent. He worked as a precision tool repairman. I have reviewed several types of documents for this case, which are listed below, including legal documents, medical records, material safety data sheets, internal Safety-Kleen documents, monitoring reports and expert reports. At the end of this report is a list of references cited herein, which are not necessarily all inclusive, but are extensive and representative of the studies and publications that support my opinions. The opinions expressed herein are my own, and were not developed in relationship to my Ohio State University service. If additional materials are provided to me after the submission of this report, then my opinions may be supplemented or changed.

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QUALIFICATIONS

As my *Curriculum Vitae* will provide in more detail, I am currently a tenured Professor in the Departments of Internal Medicine in the College of Medicine and the Department of Epidemiology at the College of Public Health at The Ohio State University. I also am an adjunct Professor at Georgetown University, adjunct Professor in the Department of Pediatrics and Child Health at the Howard University School of Medicine, and an adjunct Professor in the Department of Biological Sciences and Environmental Health at the University of the District of Columbia. At The Ohio State University, I am the Deputy Director of the OSU Comprehensive Cancer Center, having assumed this position as of September 1, 2011. Prior to that, for 11 years I worked at Georgetown University, where I was the Deputy Director of the Lombardi Comprehensive Cancer Center. Other positions that I have held in the past several years at Georgetown include Interim-Chair of the Department of Medicine, Chief of the Division of Cancer Genetics and Epidemiology in the Department of Oncology, Vice-Chair of the Department of Oncology and Associate Director for Cancer Control and Population Sciences. As such, I have been responsible for directing a multidisciplinary and transdisciplinary research program that focuses on identifying the environmental and genetic causes of cancer using epidemiology and biomarkers. Through all these activities, I am responsible for mentoring many junior and senior faculty, postdoctoral fellows, PhD, medical students, interns, residents, master's graduate students, and undergraduate students. My teaching responsibilities include, or have included, leading the academic mission of the Department of Medicine at Georgetown University, giving lectures and serving as a course director in the areas of cancer risk and epidemiology. Prior to my position at the Lombardi Comprehensive Cancer Center, I was a tenured investigator and Chief of the Molecular Epidemiology Section of the Laboratory of Human Carcinogenesis at the National Cancer Institute.

My *Curriculum Vitae* shows that I have published more than 200 papers in scientific journals, many in high-impact journals, and I serve, or have served, on the editorial boards of important journals such as *Carcinogenesis; Molecular Carcinogenesis; Journal of Cancer Epidemiology;* and, *Cancer, Epidemiology, Biomarkers and Prevention.* As evidence of the respect from my peers, I have been elected as President of the American Society of Preventive Oncology and have just completed that service, and was the first elected chair to lead the Molecular Epidemiology Group of the American Association of Cancer Research. Recently, I was elected as a Fellow of the American College of Epidemiology. Over the years, I have been the Program Chair or member of numerous program committees for national and international scientific meetings. Regularly, I am an invited speaker at national and international meetings, and at universities around the world. I also sit on various committees and panels that provide research opinions, identify funding priorities or review other investigators' research proposals about the causes of cancer. For example, I have served on the National Institutes of Health Study Section that reviews Comprehensive Centers (Subcommittee B), the NCI Clinical Trials Advisory Committee, and was a standing member of the Epidemiology and Disease Control 2 NIH study section. In the past, I have served on the National Cancer Institute's (NCI) Tobacco Research Implementation Group, NCI Lung Cancer Progress Review Group, and also on the Institute of Medicine Committee on Tobacco Harm Reduction.

Throughout my career, I have conducted research into the chemical and genetic causes of

cancer, as well as the development of tests for cancer risk and early detection of cancer. And in doing so, I regularly conduct epidemiological studies. Relevant to the case addressed here, I am an expert in the development of cancer and have published widely in this area, and have served on numerous committees that have considered this particular area of science. My publications, which include those that relate directly to some of the chemicals at issue here, have appeared in highly respected peer-reviewed journals (including those that focus on the occupational and environmental setting). Also relevant to this evaluation is that my work is considered toxicological in nature, because of the consideration of how carcinogens or cancer therapies affect the body, I frequently use laboratory methods (including animal studies), and I have published toxicology studies.

Lastly, I remain clinically active by caring for oncology patients. My clinical expertise has been recognized as I have been twice appointed to the District of Columbia Board of Medicine, which is a board that sets medical practice guidelines, grants licenses and disciplines physicians. And I have been provided awards for my work with charity patients, and have been cited as a Castle Connolly's Top Doctor for Cancer in multiple years, as recently as 2014. Thus, I consider myself an expert in cancer risk, cancer causation, carcinogenesis, epidemiology, and hematology/oncology.

DOCUMENTS REVIEWED

Legal Documents

- Declaration of Gerardo Campos (11/16/13)
- Defendant Safety-Kleen Systems, Inc.'s Objections and Responses to Plaintiffs' First Request To Produce (12/23/13)
- Defendant Safety-Kleen Systems, Inc.'s Objections and Answers to Plaintiffs' First Set of Interrogatories (12/23/13)
- Plaintiffs' Disclosure of Expert Witnesses
- Complaint (6/29/12)
- Amended Complaint (11/2/12)
- Answers to Amended Complaint - Makita (1/15/13)
- Defendant Safety-Kleen Systems, Inc.'s Answer and Defenses to Plaintiffs' Complaint (10/2/12)
- Defendant Safety-Kleen Systems, Inc.'s First Amended Answer and Defenses to Plaintiffs' Amended Complaint (12/20/12)
- Notice of Serving Plaintiff Camilla Campos' Answers to Defendant Makita's Interrogatories (7/24/13)
- Notice of Serving Plaintiff Gerardo Campos' Response to Defendant Makita's Request for Production (12/9/13)
- Notice of Serving Plaintiff Gerardo Campos' Response to Defendant Makita's Request Interrogatories (7/24/13)
- Rule 26 Initial Disclosure (11/19/13)
- Notice of Serving Plaintiff Yadira D. Veguilla Rosario's Response to Defendant Makita's Request Interrogatories (8/30/13)
- Deposition of Gerardo Campos (12/18/13)
- Deposition of Carmen B Campos Diaz (12/19/13)

- Deposition of Nydia Rosario-Colon (12/19/13)
- Deposition of Yadira VeguillaRosario (12/19/13)

Medical and other Documents
- Jose Comancho, MD
- Jose Carlo, MD
- Luis Ramos, MD
- Maria Garcia, MD
- Hato Rey, MD
- University of Puerto Rico
- Various documents produced by Makita
- Safety-Kleen Production Bates SKS_CAMP000001-000312

Expert Reports
- Su-Jung Tsai (12/10/13)
- Arthur Frank (12/13/13)
- David Goldsmith (12/13/13)
- Melvin Kopstein (12/13/13)

ALLEGATIONS

The complaint states that Mr. Campo worked from 1993 to 2010 with Safety-Kleen 105. (His declaration stated 1995 to 2010, and Makita records indicate a start date of December 4, 1995.) The complaint stated "Safety-Kleen 105 Solvent is contaminated with multiple carcinogenic chemicals, including benzene, perchloroethylene, trichloroethylene, methylene chloride, chlorinated benzenes, and polycyclic aromatic hydrocarbons." It then stated that as a result of the exposure, Mr. Campos developed chronic myelogenous leukemia. Expert reports for the plaintiff have focused mostly on a putative benzene exposure.

SCOPE OF OPINIONS AND BASIS FOR THEM

I have been asked to evaluate the medical history of Mr. Campos and provide an opinion regarding his diagnosis of CML. Also, I have been asked to provide opinions generally regarding risks for CML, and epidemiology related to work that would include exposure to mineral spirits and benzene. I have been asked if the alleged exposures could be considered to have caused or contributed to Mr. Campos' CML. I also have been asked to provide a description for the methods to assess general and individual causation of cancer, and to evaluate the methodologies, factual basis for the opinions and the conclusions of plaintiff's expert's reports. I have reviewed Mr. Campos' medical records, which forms the basis for my understanding of what his medical condition was, and his alleged and real risk factors for CML. My opinions are formulated based upon my general scientific and medical knowledge, my comprehensive literature review, my research and my clinical practice as a hematologist and oncologist. I rely upon a number of sources including general knowledge, textbooks, reports of

regulatory and review agencies, and peer-reviewed scientific studies. I have performed computerized literature searches through the National Library of Medicine (PubMed) that included search terms such as leukemia, cancer, benzene, mineral spirits, gasoline, printers, mechanics, gas station, and others. These types of activities are not very different from my regular day-to-day activities as a clinician, researcher and educator. For example, my research involves the study of cancer risk and I regularly have to interpret data and communicate such in scientific journals and to the lay public. Another example is that I frequently give lectures to the public and physicians about the causes of cancer, how to screen for it and how to prevent it.

Related to the above and my expertise, I can offer opinions about toxicology, carcinogenesis (including the development of CML), epidemiology, cancer risk and general causation. As a trained clinician, I also will offer opinions about Mr. Campos' CML and his risk factors for these, and well as a specific causation opinion.

MEDICAL RECORD REVIEW

Mr. Gerardo Campos was born on May 28, 1967. He was diagnosed with CML in November, 2011 at the age of 44. Mr. Campos has a history of Charcot Marie Tooth.

The Charcot Marie Tooth disorder originally became symptomatic around the age of 14 with weakness of the lower extremities. In 1997, he had a bilateral foot drop, and was given devices to assist him. Three cousins on his mother's side also had the disease. In 2002, it was reported that his neurological problems were worse with increased difficulty playing guitar, although his lower extremity weakness was stable. In 2005 it was stated that he was currently disabled due to his neurological disorder. Mr. Campos had nerve conduction testing on February 2, 2012, which was consistent with a demyelinating hereditary neuropathy. It was reported that he had a history of dengue fever.

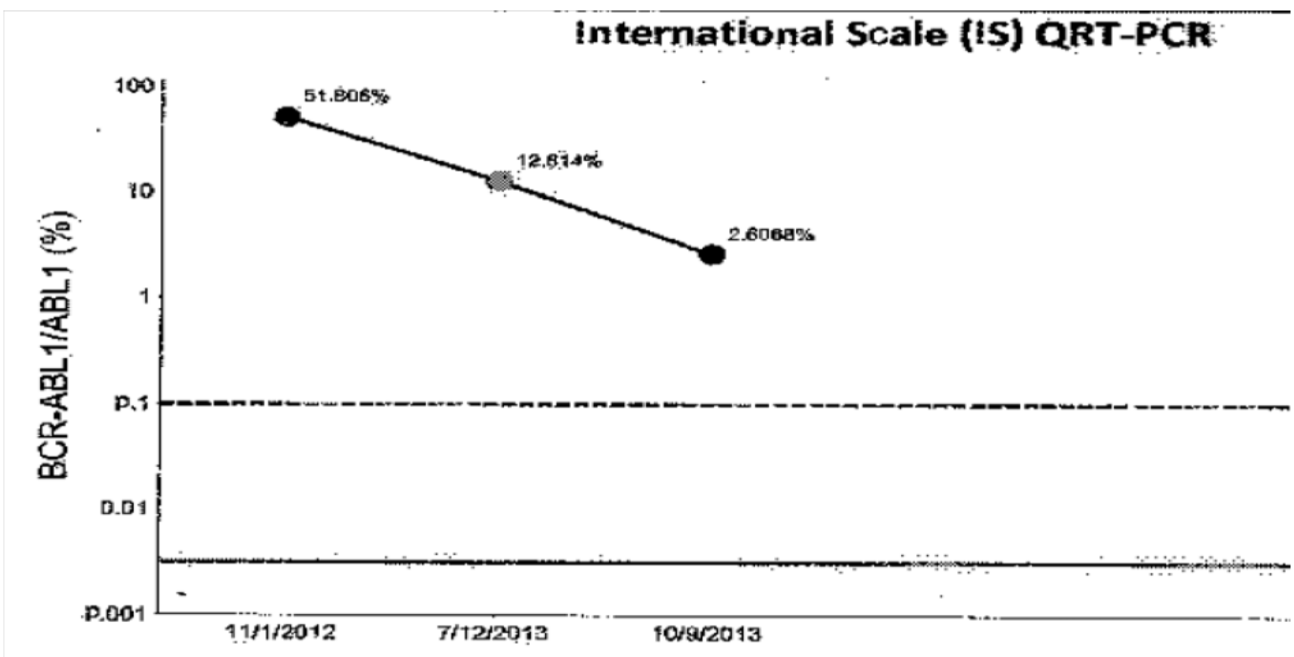
Medical records indicate that Mr. Campos was treated with Wellbutrin in 2002 and 2004. He was diagnosed with recurrent depression in 2008. In 2012, Mr. Campos was seen by a psychiatrist who diagnosed an adjustment disorder.

Mr. Campos presented for a pre-op evaluation to have papilloma removed from the groin area. He was found incidentally with a high WBC. The WBC was 76.8, platelets were 562 and the HCT was 40.8. The AST was 23 and the ALT was 71. There were promyelocytes, myelocytes and metamyelocytes observed, but no blasts. He had palpable splenomegaly. On November 8, 2011, a bone marrow was done. It was reported to have very active platelet production, be markedly hypercellular, have increased markedly megakaryocytes, dysmegakaryopoeisis, increased micromegakaryocytes, decreased erythroid series relative to the granulocytes, and a shift to the left for granulocytes with occasional blasts. It was stated that the marrow was reactive compatible with a myeloproliferative disorder. The karyotype was 46, XY t(9:22)(q34;q11.2), which was confirmed by FISH. BCR/ABL PCR was 100%. The peripheral smear had normal morphology but a shift to the left with marked leukocytosis. On November 15, 2011 it was stated he was on hydrea but was being changed to Gleevec. His WBC was 56k, platelets 543k and the HCT was 38%.

On March 12, 2012, Mr. Campos was on Gleevec. His WBC was 6.89, HCT was 44.6% and the platelets were 192k. Although around that time he had Gleevec held due to cytopenias.

On August 15, 2012, it was stated he had pancytopenia secondary to Gleevec, so he was changed to disatinib. His BCR/ABL increased from 21% to 70%. He was originally started on disatinib 100/day, but had to be decreased to 50 every other day. He remained asymptomatic according to the records. On December 12, 2012, his WBC was 3.8 and the platelets were 86k. He was again reported to be asymptomatic. The On January 16, 2013, a bone marrow was done. The report said that blasts were not identified, and that the marrow was consistent with a complete remission. The peripheral smear was reported with normal morphology. Results were similar to before, except the BCR/ABL was up to 100%.

It was stated on June 10, 2013, Mr. Campos was feeling well. On July 10, 2013, the BCR/ABL was 12%. On October 9, 2013, the WBC was 2.9, Hgb was 13.1 and the platelets were 82k. BCR/ABL was 2%. Below is a graph of his trend.



At deposition, Mr. Campos said his CML caused him to have stomach pain from inflammation of the spleen, back pain, and extreme fatigue. The symptoms reportedly started about 6 months before his diagnosis. He also said he gets a flu every month due to the chemotherapy. He reported he never had radiation and no family history of blood disorders.

Mr. Campos' wife, in interrogatories, stated: "As a result of my husband diagnosis has

been absent due to his sickness. Most of his time he is at doctors' appointments or at rest because of the disease. This means that because of his disease he misses time with me and missed special events of our family and our daughter Camila, who has only 1 year old when he wad diagnosed with the disease. Also, I miss time from work consequently, not only to be with my husband at his medical appointments but also, because of my mental health. Also my relationship with my husband has changed since his diagnostic, we are constantly worrying and we lack of sexual activity." In 2004, a discrimination complaint authored by Mr. Campos stated the he was suffering from insomnia, sexual dysfunction and eating disorders. Mr. Campos' wife corroborated her statement at deposition.

Family History: No blood diseases. Mother with breast cancer. Two aunts with breast cancer. Cousin with breast cancer. Cousin with liver cancer. Father with skin cancer.

<u>Smoking</u>
2008 - Marijuana use
2011 - quit 1 year earlier; 15 pack years

At deposition, Mr. Campos testified that he smoked beginning at age 18 and quit in 2011, with some gaps in smoking. He also testified he smoked marijuana since the age of 17, sometimes daily.

<u>Alcohol</u>
2011 - occasional beer

<u>BMI</u>
5'8"
1997 - 144 pounds
2005 - 148 pounds
2012 - 152 pounds
2013 - 160 pounds

Occupational History: Mr. Campos' declaration stated that he worked with Safety-Kleen Solvent 105 from 1995 - 2010 while employed at Makita USA (1995-2004), National Rental Sales (2006-2010) and Tool Box (2010-2011). Makita records indicated a start date of December 4, 1995, and that he was a factory service manager and then became a power tool technician. He stated that the solvent would splash on his clothes and face. He wore rubber gloves. He reported that about 2 times a month he would repair gasoline-powered equipment. At deposition, Mr. Campos stated he used the parts washer about 10 times per day, between 12-20 minutes each time. He stated that sometimes he would wear gloves provided by Safety-Kleen depending on how long he would need to wash the part. Also, he said that sometimes he would clean his hands with the solvent. At the other workplaces, he used the parts washer similarly or less.

Prior to the above, the reported work history is 1992-1994 Astro Industrial Supply that made cables for towing ships -warehouse employee and power tools technician and 1995 Ferreteria Abraham that was an industrial hardware store - power tools technician. At deposition, Mr. Campos also said he worked at a clothing store and an electrical equipment store. He denied chemical exposures for all of these jobs.

DISCUSSION

Mr. Campos has CML, which is a type of chronic leukemia. He presented incidentally with typical findings, namely an elevated white blood cell count, and without symptoms. The molecular and cytogenetic work-up confirmed the diagnosis of CML. Mr. Campos has a 9,22 translocation, which is diagnostic for CML. Mr. Campos received the diagnosis of the CML from his treating physicians, and I concur with this diagnosis, although I have not reviewed the actual pathology slides.

Leukemias are one type of many hematological malignancies. All of these are clonal disorders that are composed of a single and specific cell type. As with other types of cancers, the cells of these clonal stem cell disorders fail to differentiate and reproduce uncontrollably, crowding out space for normal bone marrow elements. Actually, leukemias also are a heterogeneous group of blood cell malignancies. They are classified as acute or chronic, and originate from either myeloid or lymphoid lineages The diagnosis of leukemia is made by examining the bone marrow with a microscope, flow cytometry, immunohistochemisty and chromosomal analysis. Among the reasons why it is important to identify the type of leukemia is that the etiology, biology, treatment and prognosis can be very different.

CML is an uncommon disorder, accounting for about 5,920 new cases in the US in 2013 [1]. This is among a total of 48,610 new cases of all leukemia and about a third as common as AML with about 14,590 cases per year. The annual incidence of CML is 1.6 cases per 100,000 adults.

CML is classified as a myeloproliferative disorder, but is very different from other myeloproliferative disorders because of its Philadelphia chromosome positivity [2-5]. All of these also have very different clinical histories and treatments, although there may be some overlap as one develops overtime. The hallmark of CML is the finding of the Philadelphia chromosome, which is a translocation of the *BCR-ABL* genes on chromosomes 9 and 22. Although CML is manifested primarily as an abnormality in the white cell lines, the chromosome abnormality is seen in all cell lines. The laboratory findings are a leukocytosis in the blood, with an increased number of neutrophil precursors, but not blasts. There is no significant dysplasia, distinguishing it from myelodysplastic syndromes. Also seen in the blood is an increase of basophils, and sometimes eosinophils. The platelet count may be elevated, but not depressed, also distinguishing it from MDS and AML. In the bone marrow, the hyperplasia of the white blood cell line is seen, without an increase in blasts unless the patient is in the later

stages of CML. There can be megakaryocytic proliferation and the megakaryocytes are small and hypolobulated.

CML clinically has three phases, namely the chronic phase, the accelerated phase and the blast phase [6]. Mr. Campos is currently in the chronic phase. Patients frequently present in the chronic phase (about 40%), without symptoms, and the disease is detected by a routine blood test [7]. Eventually, patients may complain of weakness, weight loss and discomfort due to a large spleen. The accelerated and blast phases are now uncommon due to recent therapies. The criteria for blast phase include a blast count in the bone marrow greater than 20%, depending on the criteria [6]. Evolution is usually accompanied by additional genetic abnormalities, such as an extra Philadelphia chromosome, +8, +19 or i(17q).

The Philadelphia chromosome is a reciprocal translocation from chromosome 9 to chromosome 22 that involves the *ABL1* gene on chromosome 9 and the *BCR* (break point cluster) gene on chromosome 22 [5;7]. This is termed the *BCR-ABL* translocation. The resultant gene fusion makes a protein that has tyrosine kinase activity. This protein leads to deregulated cellular proliferation, cells that are less able to adhere to the bone marrow and decreased program cell death in response to mutagens. Targeting the tyrosine kinase activity, the so-called tyrosine kinase inhibitors (TKI) is what has made the remarkable treatments available for this disease. In the past, there was an entity of Philadelphia chromosome-negative CML, but these were based on cytogenetics and molecular phenotyping now either show a cryptic translocation or the disease is not CML. The site of where the breakpoint is may influence the clinical course of CML. The breakpoint regions can also distinguish CML from CMML and ALL, which also can have the Philadelphia chromosome.

The postulated cell of origin is unclear, and while it is likely that the abnormalities start in a hematopoietic stem cell, the phenotype of the disease is thought to happen in more committed precursors of the granulocytic-macrophage progenitor pool [6].

Sometimes, other cytogenetic abnormalities are seen in CML, such as trisomy 8, isochromosome 17 and a duplicate Philadelphia chromosome [6], but these are not the type associated with leukemias thought to be caused by chemotherapy or benzene [5]. Specifically, chromosome 7 deletion occurs in less than 5% of CML cases and chromosome 5 deletions rare [8]. A search for reported cases in the National Cancer Institute CGAP database shows that there are only 27 cases are found in that database for -5 deletions and 112 cases for -7 deletions (http://cgap.nci.nih.gov/Chromosomes/Mitelman). (It is common that as CML progresses to blast phase and chromosome 7 deletions can be observed there, but -5 are still uncommon [9].)

There are several highly successful treatments for CML. Without treatment, patients with chronic phase CML will progress to the other phases in 3 - 5 years [7]. The risk for transformation was about 3- 4% per year, without modern treatments [10]. CML in blast phase is highly refractory to chemotherapy and so is rapidly fatal. While there have been earlier proposed prognostic factors for CML, such as those proposed by Sokol [7;10], these are no

longer clearly valid since the development of Gleevec. Currently, the adverse prognostic factors for patients include age greater than 60, hemoglobin less than 10, the presence of any blasts in the blood and basophils >5% in the marrow [11]. The latest treatment for CML takes advantage of the molecular changes caused by the *BCR-ABL* translocation and its tyrosine kinase activity [5;7]. The first, and still most commonly used drug is Gleevec (imatinib mesylate) [12;13]. It almost always leads to a complete cytogenetic response, about 70-96% of the time, where Philadelphia chromosome positive cells are no longer detected. The common side effects of Gleevec include nausea, diarrhea, fluid retention (including periorbital edema), bone pain and muscle cramping. Elevation in liver enzymes and dermatologic reactions are less common. There are two other drugs now available that are considered also good first line treatments, which are niotinib and dasatinib [12;14;15]. All three are relatively equivalent and are considered back-ups for each other. The choice of drug depends on the patient and the side-effect profile [13;16]. Mr. Campos had blood count issues with the imatinib and so was switched to dasatinib, without loss of efficacy.

The success of therapy is monitored by quantitative PCR for the *BCR-ABL* fusion, and the best responses are those for persons with a 3 log decrease in transcript over 12 months [17]. Conversely, increasing levels are considered relapse [18]. Also, bone marrows are done to determine cytogenetic responses. Patients are monitored for response at 2, 6, 12 and 18 months, resulting in dose changes or drug changes, as appropriate. By 12 months, there should be a complete cytogenetic response. The transcript level should decrease to below 10% or have better than a partial cytogenetic response. A complete cytogenetic response is defined as no PH-positive metaphases on a bone marrow, while partial is 1-35%; a major response is either complete or partial response, while a minor response is <100% but greater than 35% [13]. For molecular responses, a complete response is no detectable transcripts by QPCR, and a major molecular response is <0.1% or >3-log reduction. For patients failing therapy, mutation analysis is recommended to help direct therapy, e.g., specific tyrosine kinase inhibitors [13;16]

The survival estimate is 96% at 3 years and 82% at 4 years [17;19]. Now, with longer studies, 97% of patients are alive 5-8 years after therapy [13], and 67% at 10 years [11].

If a complete cytogenetic response is not achieved, then a stem cell transplantation is considered [13;20]. The only curative treatment for CML is stem cell or bone marrow transplantation [17]. But, it has been recently projected that long term survival for Gleevec is better than bone marrow or stem cell transplantation generally, which was previously the best long term option for CML [21]. Transplantation from siblings yields a 60% five year survival, and about 50% for unrelated donors. This would now be used for persons who become refractory to Gleevec and clinical trials are exhausted for newer drugs. It also is used for blast phase, and in some persons in accelerated phase who also are refractory to non-transplant treatments.

CML is more common in men than in women, and the median age at diagnosis is 65

years old [7]. It also is more common in African Americans than in Whites.

The causes of CML is essentially unknown, although there are some associations with radiation [6;22]. For example, increase risk has been reported for atomic bomb survivors, radiologists and in persons treated with radiation therapy [7;23-26]. Being overweight may also be a risk factor for CML [27]. Familial patterns for CML do not seem to exist [28].

It is not appropriate to extrapolate risks for all leukemias to any specific leukemia. The cause of CML is likely different than for acute myelogenous leukemia (AML), and appears to be chemically-resistant as an etiology [29]. For example, while cigarette smoking is a known cause of AML, there is only some evidence for increased risk for CML from cigarette smoking [30-32], but other studies are null [27;33]. In contrast, there are many studies about AML, with reported risks are about 1.5-2.0-fold [32;34-41], and a dose-response effect has been reported [27;32;36;40;42;43]. The cytogenetic abnormalities in AML related to smoking are not the type commonly observed in CML, and are not the causative abnormalities[34]. Generally, smoking is not considered a cause of CML. As another example, secondary leukemias following chemotherapy present as AML, not CML. Secondary leukemias occur following some chemotherapy or radiotherapy treatments, such as for Hodgkins lymphoma and breast cancer [44-47]. The secondary leukemias from chemotherapy often are accompanied by abnormal cytogenetics [44;48;49], which are not found in CML [29]. It also is important to note that CML is not considered a leukemia secondary to chemotherapy, and that 9,22 translocations are rare [45;50]. For example, it has been reported that the 9,22 translocation occurs in cases of secondary leukemia from topoisomerase II inhibitors, but this is uncommon [50;51]. There is essentially about 25 cases in the world's literature [50;52]. Because it is uncommon, it is unclear if these really are secondary leukemias, or a *de novo* CML. Generally, for AML versus CML, I am not aware of scientific studies that indicate that either the chromosome -5 or -7 abnormalities are common in CML (see above). Conversely, the 9,22 translocation characteristic for CML is rarely seen in cases of AML, occurring in less than 1% of adult AML [53-55], and these may be persons with previously undetected CML. (The 9,22 translocation is sometimes seen in acute lymphocytic leukemia [55].) Last, CML does not have features of dysplasia, distinguishing it from myelodysplastic syndromes and AML.

Acute leukemia secondary to benzene has been considered to follow a similar mechanism as other secondary leukemias from alkylating agents, because the same chromosomal abnormalities can be found (although not in all studies)[56;57], and so is sometimes more broadly referred to as a secondary leukemia [44;45;58]. The 9,22 Philadelphia chromosome was not reported in these studies. I am aware of one study that reported several cases with the Philadelphia chromosome, but these were mostly in people with prior CML, and there was no relationship with benzene exposure [56].

Charcot-Marie-Tooth (CMT)Syndrome: This is a hereditary disorder of the nervous system, affecting both motor function and sensation [59-61]. The estimated prevalence is about 1 in

2500 people, and is the most common inherited neurological condition. There are actually more than 50 types of CMT, affecting the myelin sheath or the axon, or both. Mutations in more than 29 genes have been identified; mutations in *PMP22*, *GJB1*, *MPZ*, and *MFN2* cause more than 90% of the disease. The pattern is usually autosomal dominant, but autosomal recessive forms also exist. This is a disease that affects peripheral nerves that result in distal muscle atrophy in the legs, decreased reflexes, foot deformities and gait problems. Hands also are involved as the disease progresses. Symptoms start in the first or second decade of life, and are progressive over life. About 20% of patients can have neuropathic pain.

METHODOLOGICAL APPROACHES TO GENERAL CAUSATION AND INDIVIDUAL RISK ASSESSMENT

There are well-established practices for considering if a chemical can cause cancer such as CML. Typical of other physicians and scientists, my initial approach before considering the individual's situation and alleged exposures is to assess if there is a relationship of the alleged exposure to the identified cancer at any level of exposure. This is done by reviewing scientific textbooks and articles, doing computerized literature searches and drawing upon my experience as a researcher, clinician and epidemiologist. The method for the determination of cancer causality is described below. It is important to assess different types of scientific data, relying on the best studies, and even though a researcher might postulate causality (e.g., as might be done through a publication of a case report, an ecological study or a case series), this is different from concluding a causal relationship of exposure to an outcome. Among the types of data that should be evaluated, human epidemiological data is substantially more reliable than laboratory *in vitro* and experimental animal data, assuming the epidemiological and other human studies are of good quality. If there is sufficient epidemiological data to make a conclusion, then experimental animal or other studies are sometimes considered only in the context of understanding biological mechanisms. If there is sufficient reason to consider that the chemical has a potential to cause the type of cancer identified for the individual or a group of individuals (target organ specificity is important), then an individual risk assessment is made to determine the doses reported in the literature that may be associated with an increased cancer risk, and in what settings. The dose, i.e., how much of a carcinogen enters the body, and then reaches the critical organs and targets within the organ, best determines an individual's cancer risk, as carcinogens clearly have a dose-response relationship.

The distinction between dose and exposure must be noted and is important. An individual might be in a room that has a chemical in the air or come into skin contact with a workplace solvent, and so has a potential exposure, but this does necessarily translate into dose, which is the amount of the agent that enters the body. Thus, one must consider that exposure may not be a sufficient marker for dose. Importantly, there is some level below which we can no

longer measure an increased risk, and so any conclusions of cancer causation for exposures below that level are speculative, unsupportable, and at best only hypothetical. (Herein, the concept of increased risk is accompanied by the conventional use of statistics and findings of statistical significance.)

The evaluation of cancer causation, i.e., can an exposure cause cancer, requires examination of different types of data and studies. Published guidelines exist for assessing causality, such as those proposed by Sir Austin Bradford-Hill [62]. These guidelines, others [63-67], and my experience allow me to conceptually develop an opinion about causation. Actually, similar principles espoused by Sir Bradford-Hill were well-applied first in the first Surgeon General's Report on smoking and health, concluding in 1964 that smoking caused lung cancer in men, and distinctions between the original Report and the recent 2014 Report are noted in the latter [67;68]. It has been argued that the Bradford-Hill criteria may be difficult to apply or have limitations [63;69], but there is an appeal for having the best possible framework to guide research agendas and study design [64;65]. Some believe that stating the statistics is sufficient to communicate causality, while not considering the level of risk, or reporting such, is not informative [66]. In some ways, the different models reflect a purely scientific perspective, while others are derived to satisfy public health needs. However, the Bradford-Hill methodology remains the most appropriate and useful for assessing general causation. It also remains the citation and methodology for the International Agency for Research on Cancer (http://monographs.iarc.fr/ENG/Preamble/index.php). As an example for applying a causation analysis, I provide a summary of smoking and lung cancer below.

Table 1 provides the Bradford-Hill criteria. While we remain true to the original writings of Bradford-Hill in many ways, there is a better understanding of how to apply the criteria after 50 years of research, and the following discussion includes several important concepts. As Bradford-Hill wrote, not all criteria are required, but today, we understand that when there is data available for any criteria, then that data cannot be ignored and some criteria are required to be fulfilled when data exists; there are some criteria that if violated would exclude the likelihood of causation, while fulfilling some may not lead to a definitive conclusion of causation without considering other criteria. Among the most important criteria is consistency in the literature, that is, do several well-designed and well-conducted epidemiology studies lead to similar findings in different populations, using different study designs. If there are more than one study available, then consistency must be met, and relying on only one or two studies among many without sufficient justification makes for at best weak support or no support for causality. It should be noted that no single epidemiological study is definitive, and the consideration of a scientific

report is performed in the context of other published studies. A determination of a biological gradient also is important, i.e., do scientific publications show a dose-response relationship, and do those doses occur in the human exposure circumstance of interest. Again, if dose-response relationships have been evaluated and must exist if so, otherwise the criteria is violated and biological plausibility also is lacking. The lack of studying a dose-response relationship, per Bradford-Hill is not required, but without it, then a causality opinion is weakly supported. Another criterion is the strength of association, which allows one to consider if the reported association in an epidemiological study is plausible (e.g., not too high or too low). Originally, Bradford-Hill, following a smoking and lung cancer causation model, considered that the higher the risk estimates, the more likely an association can occur. Now, after 50 years of epidemiological research, we understand that for some exposures and tumor types a high risk estimate is likely not true, for example in the case of a common exposure and a less common cancer as would be the case with low level benzene exposure and acute myeloid leukemia and other hematological malignancies including CML. An evaluation of temporality considers if the exposure sufficiently preceded the cancer effect to allow for latency. Specificity considers if the cancer has other reported causes and if the effect occurs in the identified target organ. Given that lung cancer was a rare disease before smoking, lung cancer and tobacco smoking is an example of specificity. Coherence refers to an evaluation and agreement of different types of scientific data (epidemiological, laboratory animal studies, cell culture models, etc.), and do they provide similar findings that lead to a mechanistic understanding of how the chemical would cause cancer in humans. Human intervention, according to Bradford-Hill are given great weight given that these are experimental situations. Such data might occur, for example, from a medical trial. Analogy looks to see if similar chemicals are known to behave similarly and what is the available scientific data for those chemicals. As an example of consistency within the epidemiological literature, tobacco smoking and lung cancer is used as an example below. In this example, in virtually every study ever done on tobacco smokers, an increased lung cancer

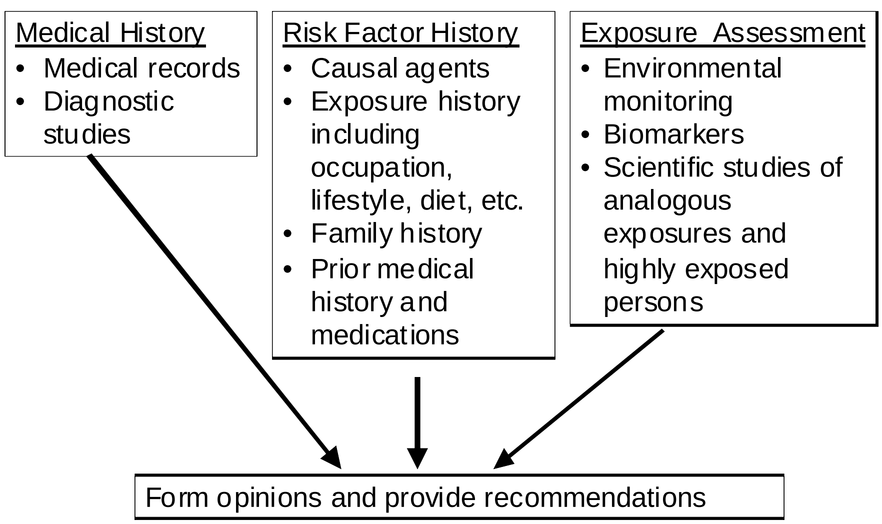
Table 1: Bradford-Hill Criteria for General Causation

- Consistency among epidemiology studies (how many good quality studies say the same thing?)
- Dose-response (does more exposure cause more disease?)
- Timing of exposure (does the cancer come after the exposure and a believable period of time?)
- Strength of Association (are results believable?)
- Specificity (is the disease unique?)
- Biologically plausible (does it make sense?)
- Coherence (is it contradictory to laboratory data?)
- Human interventions (are there reliable clinical studies to consider?)
- Analogous similarities to other toxins

rate or risk is seen. In summary, there is a general consensus for methodologies to consider what causes cancer. I generally follow the criteria set forth about 50 years ago by Sir Austin Bradford-Hill [62]. Some criterions are absolutely required (e.g., consistency and not violating dose-response). Violating some of the principals will preclude the ability to support a causal relationship (e.g., temporality).

Assuming that there is sufficient reason to believe that there is some exposure/dose that might increase cancer risk because of available scientific data, i.e., after evaluating the above criteria, then the degree and circumstances of the exposure from the literature are assessed in relation to the increased risk of the particular cancer found in a worker or group of workers. The individual risk assessment then places this into the context of potential, claimed, and/or documented exposures in an individual or group of individuals. The components of the evaluation to do this are shown in Figure 1. If the exposure level of the individual under consideration is less than that reported in the literature, or the route of exposure is different, then the chemical in question is less likely or unlikely to have caused cancer in the individual. Other unique circumstances also are considered, such as a concurrent disease, comorbidities, and other risk factors (e.g., lifestyle, diet, work place, medication) that might make the individual more or less susceptible. And also if similar exposures occurred from different sources, the relative contribution of each source is considered. Finally, the above information is integrated and a conclusion is made about the probability of causality in a person. Thus, for an individual or small group of individuals, cancer causation can only be done with an understanding of dose placed into context of the scientific literature and a causation analysis.

Figure 1: The Steps for Determining Individual Causation



Another important distinction is the difference between a risk factor and a cause. A risk factor is something that can be established from consistent epidemiology studies with statistical

significance and dose-response relationships, but a confounding factors cannot be ruled out. A cause is decided after considering multiple types of data and the application of the Bradford-Hill criteria that substantially reduces the chances of confounding in epidemiology studies. Importantly, one should not opine a cause without sufficient human evidence. (In some cases following the precautionary principle, organizations such as the International Agency for Research On Cancer makes causal conclusions based on limited human evidence and the presence of mechanistic evidence.)

HOW CANCER DEVELOPS AND THE LATENCY OF CANCER

Cancer, including hematological malignancies, is a multistage process of normal growth, differentiation and development gone awry [70-75]. It is driven by spontaneous (e.g., a defect that happens by mistake during normal replication) and carcinogen-induced genetic and epigenetic events, fueled by signals from the local microenvironment. The genes in the cells of our body are composed of deoxyribonucleic acids (DNA) that serve as a written language that programs a cell's function and provides for the building blocks to make proteins. Carcinogens bind to DNA and cause mutations and gross chromosome changes (e.g., chromosomal deletions, transfers of DNA from one chromosome to another, and chromosomal breaks) and/or alter gene expression (e.g., by affecting the switches for gene transcription). Cells normally replicate, differentiate and provide basic functions that sustain life, and then they die naturally. Some of the control of these genes that allow them to grow and function come from surrounding stromal cells and the microenvironment [74]. Mutated genes and damaged chromosomes in cancer cells, perhaps originating in a cancer stem cell can affect these basic functions, unless naturally existing safety mechanisms prevail. There are redundant DNA repair mechanisms, and cells also can be triggered to die if unrepairable DNA damage exists (a dead cell cannot go on to become cancer). If both of these mechanisms fail, however, cells may begin to replicate uncontrollably, and grow large, ultimately pushing out the normal cells and disturbing organ function. Cancer is therefore a genetic disease comprising many mutations and damaged chromosomes, as well as changes like altered methylation patterns that affect gene expression in clonally expressed cells interacting with a surrounding microenvironment [70;73;76-80]. It is thought that there are stem cells in the microenvironment that contribute to the signals that allow cancer cells to develop. As carcinogens cause cumulative damage, the probability of "initiated" cells to transform into a malignancy increases, the odds of which are increased during repeated rounds of cell replication stimulated by a lack of control in the cancer cell and signals from the surrounding stroma. The primary genes involved in driving the cancer process are proto-oncogenes and tumor suppressor genes. Proto-oncogenes are important to the regulatory mechanisms of growth, cell cycle and terminal differentiation. Activation of proto-oncogenes enhance the probability of neoplastic transformation, which can either be an early or late event. Tumor suppressor genes also code for

products that regulate cell growth and terminal differentiation. However, they have the opposite effect by limiting growth and stimulating terminal differentiation. If inactivated, then the cell may grow uncontrollably or replicate without limits defined only by blood supply and space. Cancer cells also secrete signal proteins that allow for their survival, such as blood vessel formation and allowing for metastases . The micro-environment, namely surrounding stromal cells, create signals and hormones that promote the cancer cell to grow, proliferate and provide the soil for metastases [74;75]. Inflammation and immunity is thought to play a role both for increasing risk and tumor control [81;82]. Emerging research also shows the contribution of infections, considered as the microbiome, to the development of cancer [83].

I have noted that some consider that all hematological malignancies develop from the same type of hematopoietic stem cell, and so a cause of one hematological malignancy can cause any type. This view, though, is not correct.

With the advent of new technologies, it is now recognized that cancer cells and the surrounding cells are perturbed in many ways affecting genes, gene expression, and metabolism, and that these work together to allow for a cancer cell to grow, divide and metastasize [84]. And actually, the most recent thinking about the causes of cancer is that this is a multi-system problem bridging the changes in the cells and microenvironment to the effects of the macroenvironment such as lifestyle and health care policy [85].

People are exposed to carcinogens, mutagens and other toxins every day from many sources. Humans may ingest up to 10,000 different natural pesticides and 1500 mg per day [86;87]. Other sources of mutagens and carcinogens include radiation via sunlight, in our homes, doctors offices, airplanes, etc. There are numerous carcinogens that are ubiquitous in the environment. We are exposed to potential human carcinogens such as benzene, aflatoxins, pesticides, PAHs, N-nitrosamines, heterocyclic amines and other chemicals every day in the diet (e.g., coffee, vegetables, smoked meats, and fish) [88]. Cooking produces 2000 mg/day mutagens, e.g., 1.8 ug of heterocyclic amines [88;89]. Human cells have 150,000+ DNA adducts from chemicals produced in our bodies.

Cancer is mostly a disease of aging. This is likely to be due to the redundant and protective mechanisms present in humans, e.g., metabolism, DNA repair and programmed cell death. While the DNA in our cells are constantly being exposed and affected by mutagens from birth, and before, most cancers do not develop until adulthood, and mostly much later. It is remarkable that we do not all get cancer in childhood, if the presence of mutations, or single molecules were sufficient to cause cancer. Also, it is remarkable that persons we treat with chemotherapy or radiotherapy do not all get cancer. The fact that not everyone gets cancer at early ages also is consistent with a threshold effect for accumulated genetic damage (e.g., that one molecule cannot cause cancer, and that there needs to be enough exposure to cause multiple genetic abnormalities).

Given that cancer develops from multiple genetic and epigenetic defects in the cancer cells plus support from the surrounding microenvironment, and that humans have redundant repair mechanism to preserve normal cell function, there is likely a threshold level for carcinogenesis. Clearly, cancer is a complex process that is not affected by a single molecule, as has been previously thought, contributed to by both the micro- and macroenvironment [85]. For example, as dose increases, there is increased risk to overwhelm the repair mechanisms, changes in the microenvironment and accumulate pro-oncogenic damage in cancer cells. In the regulatory arena, however, some risk assessment models follow the precautionary principle, assume that there is no threshold for genotoxic dose and cancer effect, while there is one for epigenetic effects. However, the determination of genotoxicity and epigenetic alterations is generally determined by experimental studies with unclear relevance to humans. There are no equivalent human models to conclude that a human carcinogen only works by one mechanism or the other.

Regulatory and Review Agency Classifications: Several review and regulatory agencies have considered the carcinogenic potential for chemicals cited in the complaint for this case. It is important to realize that regulatory and review processes, and the conclusions derived therein, are not applicable to the process of directly assessing past and future risk for individuals or groups of individuals. These agencies are classifying agents in order to prioritize which potential exposures should be considered for risk assessments and regulatory control. It also is important to understand that these agencies consider population cancer risks (e.g., in thousands and millions of people) and do not provide conclusions regarding individual cancer risks (or for small groups of individuals). Their conclusions are focused on protecting public health, i.e., to acknowledge that there are limitations in the scientific data and some risks might not be measurable. Their methods lead to an interpretation of data in ways that err on the side of caution and assume worse risk than can exist. While this is an important process to protect humans before we learn whether a chemical causes cancer in people, these agency methods and findings are not appropriate to support a conclusion of cancer causation in a particular individual, or to predict risk in particular individuals, or to conclude whether the chemical is carcinogenic in humans at all. Moreover, a conclusion of possible or probable carcinogenic potential for one type of cancer in a target organ does not imply that the chemical can cause cancer in other organs.

When reviewing the preambles or methodologies for all the regulatory and review agencies, it is clear that they instruct the reader to not infer individual causation from the classification assessments. In fact, they also make it clear that their classification scheme, for example labeling a chemical exposure as probable or possible human carcinogen, should not be equated with the conclusion that the exposure actually is a human carcinogen. For example, ATSDR indicates that their minimal risk levels serve as a "screening tool to help public health professionals decide where to look more closely" (http://www.atsdr.cdc.gov/mrls/index.asp). The International Agency for Research on Cancer writes: "The Monographs are used by national

and international authorities to make risk assessments, formulate decisions concerning preventive measures, provide effective cancer control programmes and decide among alternative options for public health decisions." (http://monographs.iarc.fr/ENG/Preamble/index.php). The EPA, in its IRIS assessment writes: "In general IRIS values cannot be validly used to accurately predict the incidence of human disease or the type of effects that chemical exposures have on humans. This is due to the numerous uncertainties involved in risk assessment, including those associated with extrapolations from animal data to humans and from high experimental doses to lower environmental exposures. The organs affected and the type of adverse effect resulting from chemical exposure may differ between study animals and humans. In addition, many factors besides exposure to a chemical influence the occurrence and extent of human disease." The National Toxicology Program adopts the same language (http://ntp.niehs.nih.gov/index.cfm?objectid=03CA6383-9766-1F64-6637241FE0114FE9).

IARC classifies benzene as a known cause of human cancer, but this is for acute myelogenous leukemia, and not for CML. IARC does not consider mineral spirits to be a possible, probable or known human carcinogen.

Target organ specificity: With only a few possible exceptions, chemicals exert their carcinogenic effect specifically to only one or a few organs. Target organ specificity is common and biologically plausible given that cancer arises from the combination of the abnormal clonal cells and the microenvironment around those cells. This also applies to hematological malignancies. Just as our organs are not interchangeable, the types of cancers that arise from them are different. Exposure routes allow for greater or lesser exposure at the cellular level in the target organ (i.e., different blood flow or blockage of exposure by the blood-brain barrier). Different tissues express different metabolizing proteins such as cytochrome P450s, which are "intended" by evolution to be protective and aid excretion. Different tissues have different DNA damage, repair and programmed cell death capacities. The microenvironment from adjacent cells provides signaling molecules and other hormones. Organs have different clearance mechanisms. There are some chemicals that one would predict would be multiorgan carcinogens in humans, but are not. These include phenobarbital and caffeine. If a particular chemical exposure were a multi-organ carcinogen, then these exposures would still have a consistent effect within a species. For humans, we would find consistent effects across studies, namely that all cancer-combined incidence should be increased, and we should see replication of at least some individual cancer types across studies. For any of the chemicals at issue in this case, as listed below, there is insufficient evidence to indicate that these are multi-organ carcinogens, and almost all lack sufficient evidence for cancer risk in humans

LUNG CANCER AS AN EXAMPLE OF A KNOWN HUMAN CARCINOGEN

Lung cancer is the leading cause of cancer-related death in the United States, and the second most commonly diagnosed in men and women [90]. The risk of lung cancer from smoking is well documented, as described below. It is instructive to consider the scientific data for smoking and lung cancer, to place into context the allegation by plaintiff's experts. The application of the Bradford-Hill criteria is and applicable to the evaluation of other chemicals. While this analysis focuses on smoking and lung cancer, a similar analysis for cigarette smoking and acute myelogenous leukemia also would demonstrate causality, and for occupational exposure to benzene and acute myelogenous leukemia. However, a causation analysis for CML would fail for a causation with benzene exposure.

There were an estimated 228,190 new lung cancer cases, and 159,480 lung cancer deaths in 2013 [91]. The incidence of lung cancer has been rising dramatically over other cancers, due to tobacco smoking (see below), although the rate has been declining recently (Figure 2; reproduced [90]).

The most common histological types of lung cancer are grouped together as a non-small cell lung cancer, which is further divided into squamous cell cancer and adenocarcinoma. Some people can have a mixed histology, and some may be classified simply as large cell. A less common type is small cell cancer. Until recently, squamous cell cancers were more common than adenocarcinomas in men, but this has changed recently, and adenocarcinomas are more common [92]. This is thought to be due to a change in types of cigarettes smoked, namely filtered light cigarettes. Lower tar cigarettes have been recently considered as a cause for the increased rates of adenocarcinomas [67].

Tobacco smoking is among the best examples of a human carcinogen, and is very well-documented to cause lung cancer [92;93]. In 1950, Doll and Hill [94], and Wynder and Graham [95] both reported the extremely high incidence of smoking in lung cancer patients. In fact, lung cancer was a rare disease before smoking [94]. If one is to use almost any method to assess causality, such as that proposed in the first Surgeon General's Report [96], and later articulated in more detail by Sir Austin Bradford Hill [62], then clearly the use of tobacco products causes cancer. The process for the causation analysis has been recently reviewed [67]. This conclusion comes from substantial epidemiology, laboratory animal and *in vitro* studies. It accounts for about 90% of lung cancer cases [97]. Even low levels of cigarette smoking increases lung cancer risk [98]. A summary of selected studies is shown in Table 2. Tobacco smoke contains more than 100 carcinogens and mutagens, many of which are classified as carcinogens based upon human and animal studies , the latter of which include target organ specificity. It is estimated that 20% of all cancers worldwide are attributed to smoking [99]. Smoke constituents include

PAHs, arsenic, benzene, dioxins, nitrosamines, aromatic amines, vinyl chloride, and chromium [100-103]. A dose-response relationship for cigarette smoking and lung cancer has been established in cohort studies of both men and women (Table 2). These studies show remarkable consistency. Both daily smoking amounts and duration of smoking are important contributors to risk in various models, although there are some disagreements about whether smoking per day or duration is more important [104;105]. An earlier age at initiation is a separate lung cancer risk

Figure 2: Cancer Mortality Trends

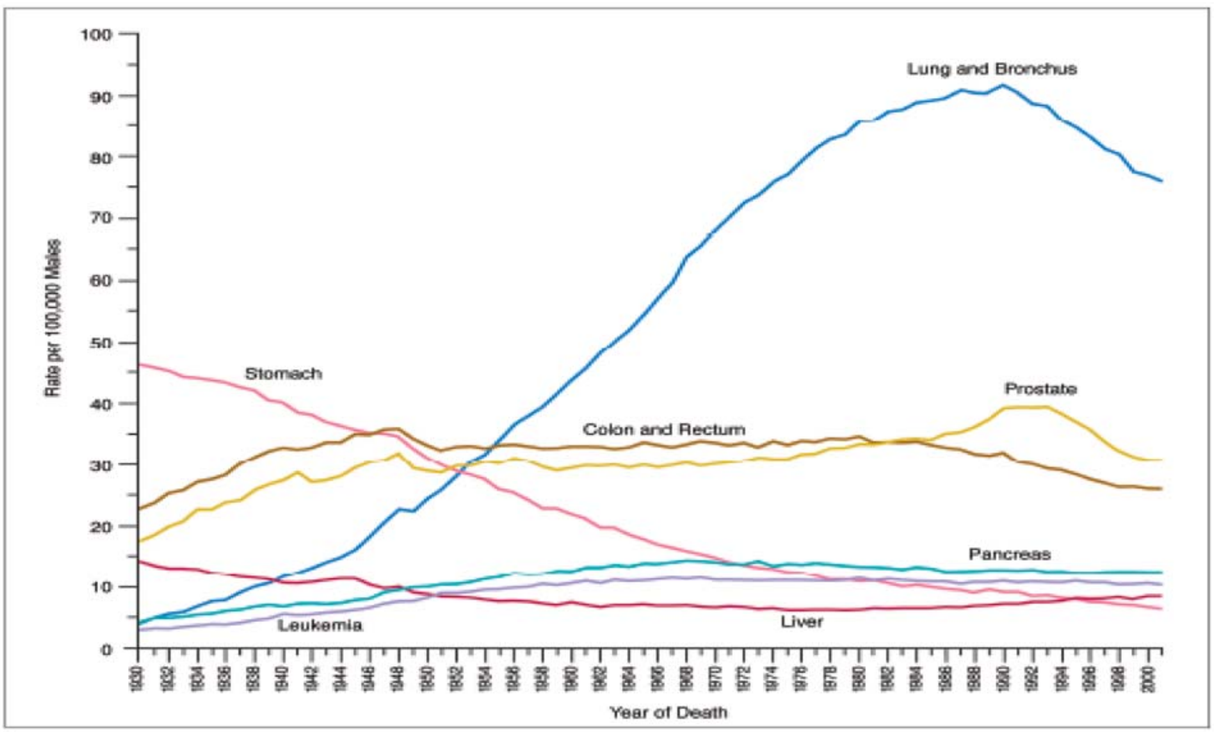


FIGURE 4 Annual Age-adjusted Cancer Death Rates* Among Males for Selected Cancer Types, US, 1930 to 2001.
*Rates are age-adjusted to the 2000 US standard population.
Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancers of the lung and bronchus, colon and rectum, and liver are affected by these changes.
Source: US Mortality Public Use Data Tapes, 1960 to 2001, US Mortality Volumes, 1930 to 1959, National Center for Health Statistics, Centers for Disease Control and Prevention.

factor [106-108]. Zang and Wynder had proposed an estimate of cumulative "tar" exposure by determining all brands used for different periods of life, the quantity per day and the milligram yields were calculated per the FTC method [109]. The reported effect of how deeply someone inhales also has been associated with an increased risk [107;108]. In a cohort of smokers with lung disease (chronic airway obstruction), about 33% of middle-aged smokers developed lung cancer after 14.5 years [110]. There is data to show that smoking unfiltered cigarettes had higher risks compared with smoking other types of cigarettes. Analyses of large cohort studies support

Table 2
Selected Lung Cancer and Smoking Studies – Consistency of Association

Cohort	**Number of subjects**	**Positive lung cancer association?**	**Dose-Response (risk estimate)**
British Doctors	34439	Yes	Yes (15)
ACS-25 State Study [111;112]	120000 men 619925 women	Yes Yes	Yes (11)
U.S. Veterans [113]	293,958	Yes	Yes (11)
Japanese Study [114]	265000	Yes	Yes (5)
ACS – 9 State Study [115]	187,783	Yes	Yes (11)
Canadian Veterans [116]	78000	Yes	Yes (NA)
Swedish Study [116]	25,444	Yes	Yes (NA)
California Study [117]	68,153	Yes	Yes (8)
MRFIT [118]	12,866	Yes	Yes (7)
Iowa Women's Health Study [119]	41,843	Yes	Yes (10)
Norwegian Study [120]	68,825	Yes	Yes (16)

this conclusion [122]. In studies of filtered versus nonfiltered cigarettes, smokers of filtered cigarettes had a decreased lung cancer risk by 30% in a French study of 1,057 lung cancer cases and 1,503 controls [123], a 2-fold lower risk in a Philadelphia study [124] and a 4-fold decrease for women in a Spanish study . Wynder and Stellman [125] reported that in 684 cases and 9,547 controls, there was a reduced risk for smokers of nonfilters cigarettes for ten years or more, although the results were not statistically significant. However, when they later reported data for 1,242 lung cancer cases compared to 2,300 controls, and accounted for increasing smoking per day after switching to lower "tar" cigarettes, they found that lung cancer risk was not reduced, and even increased in the highest levels of compensation [126]. Other studies also have reported a reduced risk for filtered cigarettes [127;128], but dose-response relationships for persons mixing their brands was harder to demonstrate [128;129]. There are some studies, however, which do not support a decreased risk for filtered cigarettes. In a population-based case-control

study, when amount of smoking was considered, there was no benefit to the filtered cigarettes [130]. Data pooled from four cohorts failed to show a statistically significant benefit for filtered cigarettes and lung cancer risk, even among different levels of smoking [131], as did another large cohort of 79,946 members of Kaiser Permanente (RR=1.03 for men and 0.65 for women, neither statistically significant), although women who used filtered cigarettes for more than 20 years had a risk of 0.36 (95%CI=0.18, 0.75) [132]. Thus, while there are a significant number of studies to indicate that smoking unfiltered cigarettes is more risky for lung cancer, this conclusion is tempered by contrasting studies. Filtered cigarettes compared to nonfiltered cigarettes are more closely associated with adenocarcinomas rather than squamous cell cancers [133], although this observation is more strongly related to women smokers [134].

Corroborating the increased risk of smoking for lung cancer are clinical trials that show that quitting reduces the incidence of lung cancer [110]. Large cohort and case-control studies also report the benefits of quitting [122]. Reducing how much someone smokes per day decreases the risk somewhat [135].

Environmental tobacco smoke (ETS), also termed passive smoking or exposure to second-hand smoke, has been estimated to cause 2,600 to 7,400 lung cancer deaths per year among non-smokers in the U.S., according to a review of 9 studies of lung cancer mortality . The initial evidence linking ETS with increased risks for lung cancer came from studies in Japan and other countries in which smoking among women is rare. The conclusion that ETS is a cause of lung cancer has been opined by several reviewers and persons conducting meta-analysis [136-140]. This is an example of how it is possible to document increased risks from low level exposure, when it occurs. In many studies, the risk of lung cancer among non-smoking women was evaluated in relation to the presence/absence of a husband who smokes. For example, Fontham, et. al., [141] reported an odds ratio of 1.5 for the association of lung cancer among lifetime non-smoking women who lived with a spouse who smoked. Janerich et al.[142] found no association with ETS in adulthood but an odds ratio of 2.0 for high levels of household tobacco smoke in childhood. Stockwell et al.[143] compared 210 women with lung cancer who were lifetime non-smokers with 301 controls assembled by random digit dialing. The maximum effect detected was an odds ratio of 2.4 (95% CI 1.1-5.3) for >40 smoke-years of exposure (with a p-value=0.004 for trend). Numerous other studies support the conclusion that ETS exposure increases lung cancer risk [136;143-145]. A recent review of 44 such studies revealed that the relative risk for lung cancer among non-smokers is between 1.16 and 1.24 for women who have a husband who smokes, relative to non-smokers whose husbands are also non-smokers [146]. Examining studies that use cotinine to classify ETS exposures, Tweedie and Mengersen used a meta-analysis approach and concluded that ETS risk was 1.17 (95%CI=1.06, 1.28) [144].

In summary, if one assesses the causation criteria by Bradford-Hill to smoking and lung cancer, every criterion is fulfilled, even at low dose exposures such as ETS . As stated above, a similar analysis could be done for cigarette smoking and acute myelogenous leukemia, as is true

for benzene and acute myelogenous leukemia, leading to a causal conclusion. However, the risk for causally relating benzene to leukemia is clearly related to dose. A similar analysis for CML and smoking, and also benzene, would demonstrate insufficient data to conclude causation.

MINERAL SPIRITS

The Safety-Kleen products used by Mr. Campos are essentially mineral spirits. Mineral spirits is a generic term for petroleum solvents, which is a complex mixture of straight and branched chained carbon compounds (aliphatic hydrocarbon compounds). There can be several Chemical Abstract Service (CAS) numbers associated with mineral spirits [147]. It is similar to, and is sometimes used synonymously with Stoddard solvent, naptha (although naphtha also can be composed of aromatic hydrocarbons), white spirits and benzine. Basically, mineral spirits and related chemicals are distilled from petroleum, and so it is a refined petroleum product. Because of the concern of potential contamination with benzene, contaminant levels have been controlled for decades, including the 1970's, and the benzene content is usually <0.1%, and typically less than 0.005% [147;148]. The Safety-Kleen 105 virgin and recycled solvents have been studied, and the benzene levels are trivial, well-below levels of federal reporting requirements on MSDS'.

Mineral spirits are widely used; it is estimated that more than 75,000 workers use mineral spirits daily [149]. With such large numbers of workers, the potential toxicity of use has been well-studied. If there were some risk of CML, or even acute leukemia, this would be known. ATSDR, in their 1995 Toxicological Profile for mineral spirits does not indicate that there is a benzene exposure related to mineral spirits [150]. ACGIH does not consider that mineral spirits contain a significant amount of benzene, citing only a single case report of a worker with aplastic anemia [151]. IARC does not classify mineral spirits as a human carcinogen. The toxicology of mineral spirits has been extensively studied [147]. Mineral spirits are not genotoxic in the laboratory, and there are no genotoxicity studies in humans that I am aware of. Mineral spirits are generally not tumorigenic in experimental animal studies, although one model uniquely is associated with adrenal tumors [147;152]. Studies of workers using mineral spirits are appropriate studies to consider for the alleged CML risk in Mr. Campos, because these typically have some low level content of benzene, and none that I am aware of report an increased risk of CML. While plaintiff's experts opine that benzene is a relevant discussion point for assessing Mr. Campo's workplace risk, actually, he worked with mineral spirits and not benzene. There is no evidence that the Safety-Kleen provided to Mr. Campos' workplace was different than any other virgin mineral spirits, and in fact, there is testing for Safety-Kleen 105 shows benzene content at trivial levels.

It is my understanding that the Safety-Kleen 105 solvent in Puerto Rico was only virgin solvent and not recycled solvent. However, even if Mr. Campos worked with the recycled solvent, my opinions would not change given the trivial amounts of benzene that occur in the

recycled solvent.

Benzene air sampling around parts washers indicate exposure levels below permissible limit and generally at background, especially after several days of use. For example, the NMAS 1995 study sampled 15 customer locations using the parts washers, including facilities that repaired automobiles, trucks, trains and motorcycles. Sampling also was done at service facilities and industrial production sites. All the air sampling in the customer sites were below permissible limits and most were not-detected. Levels decrease over time as the benzene is volatile and levels decrease rapidly within hours of use, e.g., Brinkman and Blair 1990 report: Volatile Solvent Evaporation From An Operating Parts Washer. Published research articles are in agreement for sampling of parts washer mineral spirits, air levels and how levels rapidly drop [153-155]. NIOSH also has evaluated several sites that use Safety-Kleen and elevated benzene levels were not reported, nor was benzene even expressed as a concern.

BENZENE

It has been alleged that benzene exposure in this case caused Mr. Campos to develop CML. However, Mr. Campos worked with mineral spirits, and not benzene, or a product with significant amounts of benzene. For this report, given that plaintiff's experts somehow take importance to trivial benzene content of mineral spirits, ignoring studies of mechanics or similarly exposed workers, and studies of mineral spirits and leukemia risk as discussed below, I will consider risks of benzene exposure for CML. Benzene exposures in the workplace have been extensively studied, and it was recognized early that benzene was some types of leukemia (but not lymphoma). There are numerous epidemiological studies to conclude that sufficient exposure to benzene is a risk factor for acute myelogenous leukemia (AML) [156]. However, it is important to note that there is a clear dose-response effect [157-160], which results in regulatory agencies making the determination for permissible level of workplace exposure. So, as plaintiff's experts' erroneously claim relevance that benzene is a cause of AML to opine that benzene is a cause of CML, they provide a misleading opinion because Mr. Campos was not exposed to enough benzene to cause AML, and benzene is not a known cause of CML. Thus, the discussion of benzene exposure and AML generally to support a general causation opinion for benzene an CML irrelevant and misleading. More so, to claim a level of exposure that would lead to the development of any disease in Mr. Campos, there would need to evidence that there is some level of exposure that was exceeded permissible occupational limits, and also that there were some workplace activities that exceeded those of mechanics to somehow claim that the large number of scientific studies about benzene exposure for mechanics and similar workers would not be relevant. Because, worker studies for mechanics and similarly exposed workers, as indicated below, do not establish an increased risk for CML.

Positive studies for benzene exposure and AML indicate that there is a specific level of exposure that is needed before the risk of AML becomes statistically significant. The levels of exposure to benzene in workers with potentially high exposure to benzene have been documented for industries with increased AML risk, along with the variables that would modify the exposure levels; in some series, the levels for AML need to be equivalent to at least 40 ppm-years, some report risks at 200 ppm-years. I note that some studies report an increased leukemia risk at 8-10 ppm-years, although a recent re-analysis as part of a pooled study of several refineries did not find an increased AML risk (see below) [161-166]. It should be noted that actual benzene exposures have not been measured for Mr. Campos, and there is no evidence for the level of a potential exposure from one particular product or another.

The potential for benzene exposure in many work-places has been well-documented, and there is a wide range of exposures depending on the occupation [159;167;168]. There is frequent background exposure to benzene in the general population [159;169-171]. This could be from tobacco smoke, diet, car exhaust, and gasoline filling stations. However, if benzene at low doses, e.g., at background, substantially contributes to leukemia risk, then AML or CML would be common diseases. This is not the case.

There are different ways to consider Mr. Campos' actual exposure, such as considering published studies for air monitoring and biomarker studies. Biomarker studies for benzene exposure are better than environmental monitoring or personal air sampling because they provide estimates of exposure by all routes, namely both inhalation and dermal. For example, service station attendants, analogous or worse than the exposures assumed for Mr. Campos, increase their mean breath concentrations to benzene, xylene and toluene over background levels, but being above background cannot be equated to having increased risk for disease [172;173]. For this discussion, t should be noted that Mr. Campos was a repairman who did not pump gasoline or work to repair cars, both of which would have a higher usage of product and exposure to gasoline. There are different markers that one can use for benzene exposure, namely benzene levels in blood or urine, the *S*-phenylmercapturic acid (SPMA) in urine and the *t*,*t*-muconic acid in urine (TTMA). Each has advantages and limitations [168]. Benzene levels are the direct assessment of the actual unmetabolized exposure but can vary among people based on time since exposure and metabolic rates. The SPMA and TTMA reflect exposure over a longer period of time (e.g., the half-life of SPMA is 9 hours), but both can be influenced by metabolic rates as well. The SPMA is considered more specific but there is a larger database for TTMA, which can be confounded by diet. The American Conference of Governmental Industrial Hygienists recommends monitoring with SPMA or TTMA, and have published biological exposure indexes (BEI) of 25 ug/g creatinine and 500 ug/g creatinine, respectively, for end of shift levels [174]. There are many biomarker studies that consider gas station attendants and mechanics, and some consider levels in the context of smoking. Reported biomarker levels can vary by laboratory method, and are less reliable at lower levels of exposure [149;175]. Generally, exposures for the workers are higher than nonworkers, but cigarette smoking contributes largely to levels; general

population smokers can have higher levels than workers, but this can vary by the country (some countries still allow high levels of benzene in gasoline), the amount of exposure, the presence of regulation for exposure, and the amount of smoking. Several studies report higher levels for both work and smokers, but all levels are below the ACGIH BEI [174;176-178]. Among the best studies is by Fustinoni, et. al., from Italy where 78 gas station attendants were compared to 58 referents, and smoking status was reported, where the authors reported the validation of their method [175;179]. They also reported a correlation with urine cotinine. The SPMA median levels in referent nonsmokers and smokers were 4.1 and 8.0 (ug/l) and for gasoline attendants they were 5.8 and 7.5 (ug/l), respectively (levels were not corrected for creatinine). Similar results were reported by Manini, et al, including a correlation with urine cotinine [180]. Some studies report results that SPMA and TTMA are higher in exposed workers compared to controls, but smoking was not considered [181-183]. One study in Thailand indicated that gasoline workers might have levels higher TTMA than the ACGIH BEI, but smoking was not assessed and could be high in that part of the world, and an earlier publication from the same group reported levels in men to be similar [182;184]. In summary, while gas station attendants and mechanics might have higher biomarker levels than the general population, they do not have exposures above permissible occupational limits and have levels similar to smokers, where we know that smoking does not increase the risk of CML.

Chronic myelogenous leukemia and benzene risk: Most of the studies cited above only consider benzene and acute leukemia risk, or leukemia risk in general. There also has been study for CML, and the available literature does not support the causal opinion that benzene can cause CML at some dose [170;185-187]. In a review of 10 studies, only 2 were reported positive [185]. Among studies of highly exposed workers, in the series of publications from China, no statistical increase could be found[188-190]. Also, the shoe workers in Turkey were not reported to have an increased risk of CML, including for those with high levels of exposure and pancytopenia [191-193]. For the Rinsky rubber worker studies, CML was not increased; in that study, there were only three reported cases, two of which worked less than 1 month and one had an ICD code for acute leukemia [163]. Other rubber worker studies are null for CML [185;194-196]. Another study of leukemia that reported levels of benzene exposure do not find increased numbers of CML patients [197]. For the petroleum industry, where CML also was studied, null results has been reported [185;198-207], or inferred as null [208;209]. Recently, Schnatter and colleagues conducted a pooled analysis of 3 refinery worker cohorts and did not find an increased risk for CML; there was one analysis that was positive at lower levels of exposure but not higher, and was inconsistent with the other findings in the study [160]. Workers in the chemical industry and other industries with benzene exposure were null, or inferred as null for CML [210-214].

Consideration of other occupations for exposure to benzene at low levels, such as printers, painters and mechanics are helpful for understanding Mr. Campos' risks. These occupations are not considered to be at increased risk for CML, or even leukemia generally;

most or all studies within groups are null that I am aware of [215-219], with only two exceptions [216;220].

A large meta-analysis by Wong and Raabe in 1995, based on 208,741 petroleum workers from the U.S. and Canada, with 4,665,361 person years, 56,441 deaths, and 19 cohorts, found that the SMR for AML was only 0.89 (95% CI= 0.0.68, 1.15) [221]. Among the 19 cohorts reported, none had a statistically increased incidence of CML. Combined in different ways by geography, the meta-analysis did not indicate an increased risk, statistically significant or otherwise.

Vlaanderen and colleagues recently published a meta-analysis for benzene-exposed workers and CML. Their conclusion was "Although limited by low statistical power, the current meta-analysis provides support for a possible association of occupational exposure to benzene and the risk of CML.[22]. Thus, in the context of individual risk assessment, this paper refutes a positive causation opinion. The authors analyzed the data in different ways in order to provide importance to different approaches, and what the considered as the most reliable provided null results. They wrote: "The highest study quality stratum for AML significance and exposure quality showed an elevated but non-significant increased mRR (1.40; 95% CI: 0.86–2.27, and 1.68; 95% CI: 0.74–3.84, respectively)." The only positive analysis actually was for more recent studies, which is the inverse for what would be expected with workers having a higher exposure in the past. (The authors, though, also noted that these would have more certain diagnoses.) Importantly, for all the 17 studies cited by the authors, none were statistically significant.

Other meta-analyses over the last several years also are null, and use either different methodologies, including an assessment of case-control studies, and/or include additional studies [158].

I am aware of a review article published in 2006 by Myron Mehlman [222]. This publication is essentially an incomplete review of the literature that takes great weight in noting only that CML cases are reported in cohorts without consideration to statistics, similar to inappropriately relying on case-reports for causation opinions. There are a few statistically significant reported results in the review, but virtually all of these do not even study CML, or were falsely cited as being statistically significant. The Mehlman review was specifically discussed by the Vlaandaren, et. al., researchers [22], who discounted the Mehlman conclusions saying that no data synthesis was conducted. Clearly, if CML were to be associated with benzene exposure, given all the study of benzene and leukemia, it would have been identified and CML would not be such a rare disease.

PLAINTIFF'S EXPERTS' OPINIONS

Su-Jung Tsai (12/10/13): Dr. Tsai opines that Mr. Campos was exposed to perchloroethylene above occupational limits by inferring an odor threshold from mineral spirits. This is not an accepted practice for assessing either an STEL or 8 hour TWA. She provides no data for an association for perchloroethylene and CML generally, or specifically at the levels of exposure she guesses at. More so, I am not aware that perchloroethylene is an issue in this case, or even present in the virgin Safety-Kleen 105 that probably used by Mr. Campos. For benzene, there is no specific assessment of exposure, and Dr. Tsai erroneously cites to the Vlaanderen meta-analysis of CML to support her opinion; the authors stated that their analysis provides support for only a possible association and that their best evidence provided a null result [22].

Arthur Frank (12/13/13): Dr. Frank opines that Mr. Campos developed CML from his workplace. There is no discussion of the scientific literature and no report of a methodology. He cites only to Mehlman [222], which, is not an authoritative work and is in contrast to that of researchers in the field, as cited above via several meta-analyses. Importantly, Dr. Mehlman published his opinions in 2006, and so there was no benefit to the more recent studies a discussed above. The weak reliance on this publication is discussed above.

Dr. Frank apparently confuses CML with other forms of leukemia and apparently does not recognize the distinct features of the disease and etiologies.

Dr. Frank also opines that cigarette smoking contributed to Mr. Campos developing CML, although this is inconsistent with current scientific opinion. However, if Dr. Frank were not wrong in his opinion, he would have to conclude that smoking was a major risk factor, and he would not be able to say that Mr. Campos would not have developed CML, but for the alleged work-place exposures. Dr. Frank claims that smoking would lead to a small benzene exposure, but how he makes this comparison to the workplace is unclear and fails to consider smoking behavior and direct inhalation of cigarette smoke carcinogens.

David Goldsmith (12/13/13): Dr. Goldsmith provides a general and specific causation opinion for benzene and "mineral oils/solvents" exposure and CML. Like Dr. Frank, he confuses the leukemias and considers them all the same. He cites to IARC, who never claims a causal relationship for benzene to CML. His discussion of "mineral oils/solvents" is somewhat puzzling as these are different chemical mixtures with different toxicities. Dr. Goldsmith cites to Mehlman, which, as indicated above are not authoritative by any means, and provide contrary opinions to experts in the field. He also cites to a publication by Polychronakas, actually, makes no statements about benzene exposure and CML, and so it is puzzling why Dr. Goldsmith relies upon that work.

Dr. Goldsmith cites to specific publications that do not support his opinions or he miscites them. For example, he cited to the Schnatter 2012 publication [160] as supporting his opinion, which it does not. The same is true for the study by Yin, 1996 [190], although in this case, Dr. Kaufman did indicate that the study was null. In sum, the only research study cited by him that was statistically significant was the study by Adekoke, et al. 2003 [216], which

contradicts the literature and fails to establish consistency. There were no studies cited by him about mineral spirits.

Dr. Goldsmith does not cite to any methodology for formulating his opinions.

Melvin Kopstein (12/13/13): Dr. Kopstein provides an exposure assessment. He does this based on indirect evidence and does not cite to studies with actual measurements, as indicated above. There are also issues with using greatly exaggerated benzene content levels in virgin SK105. As a result, the alleged exposures are grossly inconsistent with studies that I cite above, both for exposure and for leukemia risk generally. Importantly, Dr. Kopstein provides only an exposure estimate for peak exposures and not cumulative exposure exceeding OSHA TWA limits. This is insufficient evidence to rely upon for a specific causation method. He states that Mr. Campos cumulative exposure was in excess of 2-3 ppm years, which is insufficient to increase the risk of leukemia of any type at that level.

CONCLUSIONS

1. Mr. Campos was diagnosed with chronic myelogenous leukemia. I have no particular reason to question the diagnosis. There are no unusual aspects of Mr. Campos' disease to implicate an unusual etiology.

2. The causes of CML are essentially unknown, and so virtually all patients with CML do not have identifiable risk factors and a cause is never understood. However, simply because there are no identifiable risk factors, it is not appropriate to conclude that the workplace caused the CML because "something must have done it".

3. There are many types of leukemia. It is inappropriate to consider them all the same in the context of risk.

4. Mr. Campos was a precision tool technician, which would have had activities similar to mechanics. There are many studies of mechanics and gas station attendants that can be considered to understand his workplace risks as an analogy. The literature does not implicate an increased risk for CML for these types of workers or workers who work with similar solvents and degreasers.

5. The allegation in this case is that Mr. Campos developed CML as a result of working with Safety-Kleen 105. This Safety-Kleen product is essentially mineral spirits. Many workers use mineral spirits; as an exposure there are scientific studies to consider. Mineral spirits are not considered a cause of CML. Plaintiff's experts make opinions about benzene, but Mr. Campos did not work with benzene. Rather, he worked with mineral spirits. The benzene content of mineral spirits is well-known and is trivial. It is

inappropriate to focus on benzene exposure for workers who work with mineral spirits, even if benzene was a cause of CML.

6. Mr. Campos had a trivial level of benzene exposure that was likely not above background and likely not above permissible limits, based on available studies. Benzene and leukemia risks have been extensively studied. If benzene was a cause of CML, we would know this. If benzene caused CML, it would not be a rare disease. After almost 50 years of study, contemporaneous researchers do not conclude that benzene is a cause of CML.

7. I generally follow Bradford-Hill criteria for general causation to consider levels of exposure and workplace activities for Mr. Campos, and for specific causation methodology as described herein. Understanding exposure within a general and specific causation are both very important and plaintiff's experts make wild assumptions. It is my opinion that Mr. Campos did not develop CML as a result of working at Makita or elsewhere where Safety-Kleen parts washers were used.

8. Plaintiff's expert, Dr. Kopstein, provides an exposure estimate that is fundamentally flawed, wrong and inconsistent with scientific studies. And given the lack of support to conclude that benzene is a cause of CML, the alleged exposures actually are irrelevant.

9. I have reviewed the plaintiff's experts' reports. I fail to discern a scientifically acceptable methodology for assessing individual or general causation. I note the lack of studies cited by them that support their opinion. They want to rely on studies of leukemia generally, but this is inappropriate and flawed. They fail to consider dose, even that alleged by Dr. Kopstein, in their opinions; not a single study is cited that show that CML risk is increased at the levels of exposure opined by Dr. Kopstein.

10. The above opinions I hold to a reasonable degree of medical and scientific certainty. If you have additional questions, I will address those. If additional documents or materials are brought to my attention, then I reserve the right to modify or supplement my opinions.

Sincerely,

Peter G. Shields, M.D.
Professor of Medicine and Oncology

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